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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009.809	04/26/2002	Ronit Eisenberg	30836	1519

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Arlington, VA 22215

EXAMINER

CROWDER, CHUN

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/009,809

Applicant(s)

EISENBERG ET AL.

Examiner

Chun Crowder

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05/01/2006, 06/28/2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44,46,52-56,59,60,63-70 and 72-80 is/are pending in the application.
- 4a) Of the above claim(s) 44,46,52-56,59,60,75 and 76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 63-70, 72-74, and 77-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/01/2006 has been entered.

2. Applicant election of Group A, without secondary complex, SEQ ID NO:1 as the first agent with first segment being SEQ ID NO:3, and condition of asthma, filed 06/28/2006, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-43, 45, 47-51, 57-58, 61-62, and 71 have been previously canceled.

Claims 75-80 have been previously added.

Claims 44, 46, 52-56, 59-60, 63-70, and 72-80 are pending.

Claims 44, 46, 52-56, 59, 60, 75, and 76 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. 1.142(b), as being drawn to nonelected invention.

Claims 63-70, 72-74, and 77-80 are currently under consideration, as they read on the elected species of Group A, without secondary complex, SEQ ID NO:1 as the first agent with first segment being SEQ ID NO:3, and condition of asthma.

3. Applicant's claim for domestic and foreign priority is acknowledged. The priority application PCT/IL00/00346 and ISREAL 130526 upon which benefit is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

The specification on page 1, line 1 should include a specific reference to the priority application PCT/IL00/00346 for which benefit is sought and the status of the instant application is a 371.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. Applicant's IDSs, filed 06/18/2005 and 06/19/2005, are acknowledged and have been considered.

6. The application is required to be reviewed and all spelling, TRADEMARK, and like error corrected.

Trademarks should be capitalized or accompanied by the TM or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

In addition, applicant is required to review the entire instant application for compliance with the Sequence Rules.

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7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 63-70, 72-74, and 77-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims recite "preventing mast cell degranulation in a subject".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only that the claimed complex comprising SEQ ID NOs:1 and 3 is able to inhibit histamine secretion induced by compound 48/80 by mast cell to 25% maximal response at concentration of 600 µg/ml (e.g. see Results on pages 17-20 and Figure 4 of the instant specification).

The state of the art recognizes that the effect of cell-penetrating peptides can be unpredictable due to limited knowledge of the mechanisms associated with mast cell exocytosis. For example, Jones et al. (Biochimica et Biophysica Acta 2005. 1745:207-214) teach that peptide KNNLKECGLY mimicking the Gi3a carboxy terminal amino acid residues 346-355 had been shown to inhibit mast cell secretion. However, KNNLKECGLY does not inhibit the secretion of the β-hexoseaminidase from mast cell line RBL-2H3, and in addition shows opposite effect by synergistically promoting β-hexoseaminidase secretion with stimulant MP (see entire document, particularly Results on pages 210-212).

In view of the lack of predictability of the art to which the invention pertains, working examples, the state of the art teachings, undue experimentation would be required to practice the claimed invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 63, 66-70, 72-74, and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50) in view of Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746).

Holgate et al. teach that mast cells degranulation has long been associated with asthma and pharmacological agents that can suppress the release of mast cell mediators have been shown to be clinically effective in treating IgE-dependent asthma and other forms of asthma where IgE dependent mechanisms have not been invoked (see entire document, particularly pages 40-47).

The reference teachings differ from the claimed invention by not describing a complex having peptide having amino acid sequence of SEQ ID NO:3 linked to peptide of SEQ ID NO:1.

However, the role of the peptide KNNLKECGLY (SEQ ID NO:1) in inhibiting mast cell degranulation was well known at the time the invention was made. For example, Adridor et al. teach that synthetic peptide KNNLKECGLY corresponding to the C-terminal end of protein $G\alpha_{i3}$ inhibits permeabilized mast cell degranulation induced by synthetic compound 48/80 (see entire document, particularly page 1570 and Figure 2). Adridor et al. further teach that peptide KNNLKECGLY was ineffective when added to intact cells indicating that the target for the peptide was intracellular (e.g. see pages 1570-1571).

The methods for importing biological active molecules into cells were also well known in the art at the time the invention was made. Lin et al. teach a complex comprising importation competent signal peptides, such as membrane-permeable signal peptide of AAVALLPAVLLALLAP derived from Kaposi fibroblast growth factor, linked to a biological active molecule such as a peptide can be administered ex vivo or in vivo to treat diseases (see entire document, particularly Description of the Preferred Embodiments on columns 3-11).

Lin et al. further teach that importation competent signal peptides can be linked to the biological active molecule by peptide bond (e.g. see column 7). Furthermore, Lin et al. teach that the importing methods use mechanisms naturally occurring in cells thus avoiding damaging the target cells and can be used to import molecules into large numbers of cells including organs providing treatments of diseases (e.g. see columns 1 and 2).

It would thus have been obvious to the ordinary artisan at the time the invention was made to develop methods of inhibiting mast cell degranulation using synthetic peptide KNNLKECGLY corresponding to the C-terminal end of protein $G\alpha_{i3}$ linked to a importation competent signal peptide AAVALLPAVLLALLAP derived from Kaposi fibroblast growth factor for intracellular delivery. The ordinary artisan would have been motivated to do so because mast cell degranulation was associated with asthma and pharmacological agents that can suppress the release of mast cell mediators have been shown to be clinical effective, and synthetic peptide KNNLKECGLY targeting intracellularly was a well known agent in inhibiting mast cell degranulation and importation competent signal peptide AAVALLPAVLLALLAP could be linked to peptides to facilitate delivery peptides into cell using naturally occurring mechanisms.

Given the teachings of Holgate et al regarding the role of mast cell degranulation in asthma, and the teachings of Adridor et al. and Lin et al. providing the method of inhibiting mast cell degranulation by synthetic peptide KNNLKECGLY and methods of delivering biological molecule into cell using of importation competent signal peptide AAVALLPAVLLALLAP, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed methods.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50) in view of Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746) as applied to claim 63 above, further in view of Avruch et al. (US Patent 6,103,692) and Jackson et al. (J. Am. Chem. Soc. 1994. 116:3220-3230).

The teachings of Holgate et al, Adridor et al, and Lin et al have been discussed, *supra*.

The reference teachings differ from the claimed invention by not describing cyclization and succinyl residue at the N terminus of the peptide.

However, methods of modifying peptide mimics for improved efficiency were well known in the art at the time the invention was made. For example, Avruch et al. teach useful succinylation of peptide increases its passage through the hydrophobic cellular membrane (see entire document, particularly columns 12-14). Jackson et al. teach cyclization is a highly successful strategy for restricting the conformation of peptides and can give rise to impressive gains in affinity, receptor subtype specificity and restriction of conformational mobility (see entire document, particularly Introduction on page 3220).

It would thus be obvious to the ordinary artisan at the time the invention was made to modify the peptide by cyclization and succinylation for advantages such as increase passage through cell membrane, enhanced affinity, receptor subtype specificity and restriction of conformational mobility. The ordinary artisan would have been motivated to do modify the peptide for use in inhibiting mast cell degranulation.

Given the teachings of Holgate et al, Adridor et al, and Lin et al, regarding the role of the peptide in inhibiting mast cell degranulation, and the teachings of Avruch et al and Jackson et al, providing the advantages of peptide modifications such as cyclization and succinylation, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 63-70, 72-74, 77-80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending USSN 10/465,826, and claims 1-15 of the copending USSN 11/214,588.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and copending claims are drawn to the same or nearly the same methods of treating/preventing inflammatory diseases via preventing mast cell degranulation comprising administering the same or nearly the same anti-allergic agents/peptide complex. The copending methods rely upon the same or obvious variants of species of the therapeutic agent comprising SEQ ID NO:3 and SEQ ID NO:1; thereby rendering the copending claims anticipatory or obvious over one another.

Given that all claims of the copending USSN 10/465,826 previously withdrawn from consideration under 37 C.F.R. 1.142 have been rejoined and fully examined for patentability under 37 C.F.R. 1.104, all copending claims (claims 1-44) have been included in the provisional obviousness-type double patenting rejection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.

Patent Examiner

July 13, 2006

Phillip Gambel
PHILLIP GAMBEL, PH.D.
PRIMARY EXAMINER
TC 1600
7/13/06